

We claim:

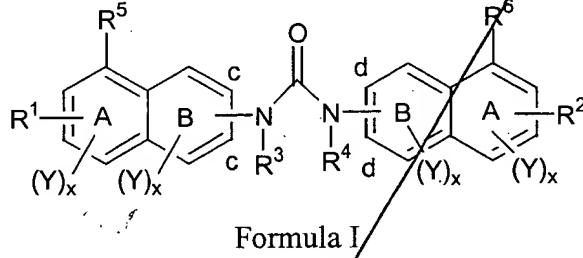
1. A method of treating a metabolic disorder in a person induced by treatment of the person with an HIV protease inhibitor, comprising administering to the person a therapeutically effective dose of an insulin receptor-activating compound that is not insulin, or a pharmaceutically acceptable salt thereof.

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2. The method of claim 1, where the metabolic disorder induced by treatment with an HIV protease inhibitor is selected from the group consisting of insulin resistance, hyperglycemia, diabetes, ketoacidosis, lipodystrophy, and hypertriglyceridemia.

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3. The method of claim 1, where the insulin receptor-activating compound is a



wherein:

R^1 and R^2 are substituents on the A ring and are, independently, $-SO_2NR^7_2$, $-C(O)NR^7_2$, $-NR^7SO_2R^7$, $-NR^7C(O)R^7$, $-SO_2OR^7$, $-C(O)OR^7$, $-OSO_2R^7$, or $-OC(O)R^7$,

20 R^3 and R^4 are, independently, hydrogen or lower alkyl, or R^3 and R^4 together
are $-(CH_2)_2-$, $-(CH_2)_3-$, or $-(CH_2)_4-$,

R^5 and R^6 are, independently, hydrogen, lower alkyl, substituted lower alkyl, cyano, halo, nitro, $-SR^8$, $-C(O)R^8$, $-SO_2OR^8$, $-OSO_2R^8$, $-SO_2NR^8_2$, $-NR^8SO_2R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8_2$, $-NR^8C(O)R^8$, $-OR^8$, or $-NR^8_2$.

each R^7 and R^8 is, independently, hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, aryl(lower)alkyl, substituted

*Sub
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S*

aryl(lower)alkyl, heteroaryl(lower)alkyl, substituted heteroaryl(lower)alkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl,
 each Y is a non-interfering substituent,
 each x is, independently, 0, 1 or 2, and
 the urea linker connects a carbon which is designated c with a carbon which is designated d,
 or a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof.

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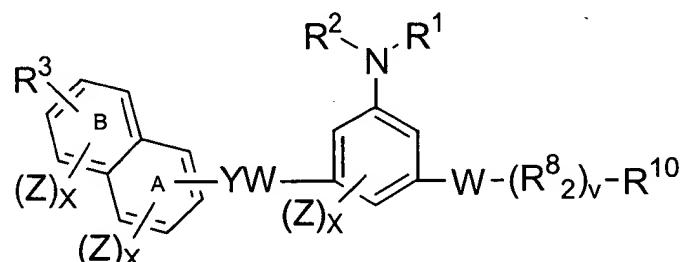
4. The method of claim 3, wherein no Y is linked to a naphthalene ring via an azo linkage in the compound.

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5. The method of claim 3, wherein, where R^1 and R^2 are both $-SO_2OH$,
 (i) no Y is $-SO_2OH$;
 (ii) neither R^5 nor R^6 is $-SO_2OR^8$ or $-OSO_2R^8$; and
 (iii) where no $(Y)_x$ is $(Y')_{x'}$, wherein x' is 1 or 2 and Y' is a halo radical, R^5 and R^6 are not both selected from the group consisting of hydroxy and hydrogen.

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6. The method of claim 1, where the insulin receptor-activating compound is a compound of Formula II



Formula II

wherein:

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R^1 and R^2 are, independently, hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, $-C(O)R^4$, $-C(O)OR^4$, $-C(O)NR^4R^5$, $-S(O)_2R^4$,

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-S(O)₂OR⁴, heteroaryl, substituted heteroaryl, heterocyclyl, substituted heterocyclyl, aryl(lower)alkyl, substituted aryl(lower)-alkyl, heteroaryl(lower)alkyl, substituted heteroaryl(lower)alkyl, or lower alkenyl, or R¹ and R² together with the conjoining nitrogen are C₃-C₉ heteroaryl, C₃-C₅ heterocyclyl, or -NO₂,

R³ is a substituent on the B ring and is -SO₂OR⁶, -C(O)OR⁶, -SO₂NR⁶₂, -C(O)NR⁶₂, or tetrazole;

each linker -WY- between the naphthyl and phenyl intersects the A ring on the naphthyl and is, independently, -C(O)NR⁷-, -NR⁷C(O)-, -C(O)O-, -OC(O)-, -CH=CH-, -NR⁷CH₂-, -CH₂NR⁷-, -NR⁷C(O)NR⁷-, -NR⁷C(O)O-, -OC(O)NR⁷-, -NR⁷SO₂O-, -OSO₂NR⁷-, -OC(O)O-, -SO₂NR⁷-, -NR⁷SO₂-, -OSO₂-, or -SO₂O-,

each R⁴ and R⁵ is, independently, hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, aryl(lower)alkyl, substituted aryl(lower)alkyl, substituted heteroaryl, heteroaryl, heteroaryl(lower)alkyl, substituted heteroaryl(lower)alkyl, heterocyclyl, substituted heterocyclyl, or lower alkenyl,

each R⁶ and R⁷ is, independently, hydrogen or lower alkyl,

each R⁸ is, independently, hydrogen, lower alkyl, substituted lower alkyl, aryl(lower)alkyl, substituted aryl(lower)alkyl, substituted heteroaryl, heteroaryl, heteroaryl(lower)alkyl, substituted heteroaryl(lower)alkyl, heterocyclyl, substituted heterocyclyl, lower alkenyl, nitro, halo, cyano, -OR⁹, -SR⁹, -C(O)R⁹, -OC(O)R⁹, -C(O)OR⁹, -NR⁹₂, -C(O)NR⁹₂, -NR⁹C(O)R⁹, -OSO₂R⁹, -SO₂OR⁹, -SO₂NR⁹₂, or -NR⁹SO₂R⁹,

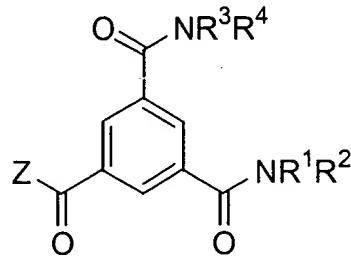
each R⁹ is, independently, hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heteroaryl(lower)alkyl, substituted heteroaryl(lower)alkyl, heterocyclyl, substituted heterocyclyl, aryl(lower)alkyl, or substituted aryl(lower)alkyl,

each Z is a non-interfering substituent,

each x and v is, independently, 0, 1, 2 or 3, and
R¹⁰ is aryl, substituted aryl, heteroaryl, or substituted heteroaryl,
or a pharmaceutically acceptable salt thereof, optionally in the form of a single
stereoisomer or mixture of stereoisomers thereof.

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7. The method of claim 1, where the insulin receptor-activating compound is a
compound of Formula III



Formula III

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wherein:

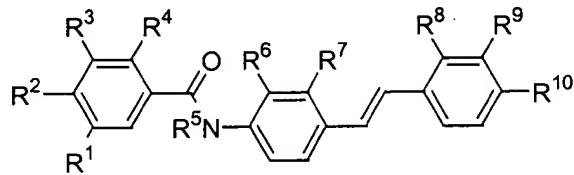
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R¹ and R² are, independently, hydrogen, lower alkyl, substituted lower alkyl,
aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclyl,
substituted heterocyclyl, aryl(lower)alkyl, substituted aryl(lower)-alkyl,
heteroaryl(lower)alkyl, substituted heteroaryl(lower)alkyl, or lower
alkenyl, or R¹ and R² together with the conjoining nitrogen are C₃-C₉
heteroaryl, or C₃-C₅ heterocyclyl,

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Z is OH, halo, OR¹ or NR¹R²,
or a pharmaceutically acceptable salt thereof, optionally in the form of a single
stereoisomer or mixture of stereoisomers thereof.

8. The method of claim 1, where the insulin receptor-activating compound is a compound of Formula IV



Formula IV

5 wherein

R¹, R³, and R⁴ are, independently, hydrogen, lower alkyl, substituted lower alkyl, halo, hydroxyl, substituted alkyloxy, carboxyl, -NR¹¹R¹², or -C(O)NR¹¹R¹²,

R² is hydrogen, lower alkyl, substituted alkyl, halo, hydroxyl, alkoxy, substituted alkyloxy, carboxyl, -NR¹¹R¹², -NR¹¹C(O)R¹², or -C(O)NR¹¹,

10 R⁵ is hydrogen, lower alkyl, substituted lower alkyl, or aryl,

R⁶ and R⁷ are, independently, hydrogen or carboxyl,

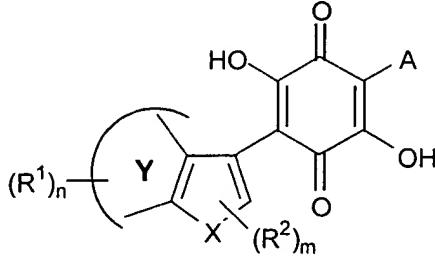
R⁸ and R⁹ are, independently, hydrogen, lower alkyl, substituted lower alkyl, halo, hydroxyl, alkoxy, carboxyl, -NR¹¹R¹², or -C(O)NR¹¹R¹²,

R¹⁰ is lower alkyl, substituted lower alkyl, halo, carboxyl, -C(O)NR¹¹R¹²,

15 R¹¹ and R¹² are, independently, hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, aryl(lower)alkyl, substituted aryl(lower)alkyl, heteroaryl-(lower)alkyl, -substituted heteroaryl(lower)alkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl-C(O)-aryl, or aryl, or a pharmaceutically acceptable salt thereof, optionally in the form of a single

20 stereoisomer or mixture of stereoisomers thereof.

9. The method of claim 1, where the insulin receptor-activating compound is a compound of Formula V



Formula V

5 wherein

Ring Y represents a 5-6-membered aryl or heteroaryl fused ring, which is optionally substituted with 1-4 groups selected from R¹;

X represents O, S(O)_m or N, wherein m is 0, 1 or 2;

A represents a member selected from the group consisting of:

10 (a) a 6-10-membered mono-or bicyclic aryl group,

(b) a 5-6-membered isolated monocyclic heteroaryl group,

(c) a 9-10-membered bicyclic heteroaryl group, attachment to which is through a 6-membered ring, or

(d) an 8-membered bicyclic heteroaryl group, the heteroaryl groups having 1-4

15 heteroatoms selected from O, S(O)_m and N, said aryl and heteroaryl groups being optionally substituted with 1-3 R¹ groups;

R¹ is independently selected from:

halo, -OH, -C₁₋₁₂alkyl(R²)₃, -C₂₋₁₀alkenyl(R²)₃, -C₂₋₁₀alkynyl(R²)₃, -C₆₋₁₀aryl(R²)₃,

-heteroaryl(R²)₃, -heterocyclyl(R²)₃, -NH₂, -NHC₁₋₆alkyl(R²)₃,

20 -N(C₁₋₆alkyl(R²)₃)₂, -N₃, -OC₁₋₆alkyl(R²)₃, -S(O)_mH, S(O)_mC₁₋₆alkyl(R²)₃,

-CHO, -C(O)C₁₋₆alkyl(R²)₃, -CO₂H, -C(O)OC₁₋₆alkyl(R²)₃,

-C(O)SC₁₋₆alkyl(R²)₃, -C(O)NH₂, -C(O)NHC₁₋₆alkyl(R²)₃,

-NHC(O)C₁₋₆alkyl(R²)₃, -S(O)_mNH₂, -NHS(O)_mC₁₋₆alkyl(R²)₃,

-S(O)_mNHC₁₋₆alkyl(R²)₃ and -S(O)_mN(C₁₋₆alkyl(R²)₃)₂

wherein m is 0, 1, or 2;

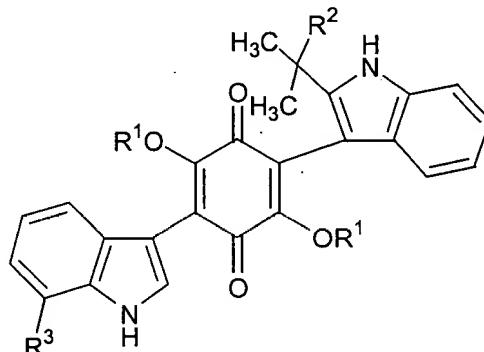
R² is independently selected from:

H, OH, halo, -C₁₋₄ alkyl, -C₂₋₄ alkenyl, -C₂₋₄ alkynyl, -CF₃, -OCF₃, -NO₂, -N₃, -CHO,
 -OC₁₋₆ alkyl, -S(O)_mC₁₋₆ alkyl, -NH₂, -NHC₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂,
 -C(O)C₁₋₆ alkyl, -CO₂H, -CO₂C₁₋₆ alkyl, -C(O)NH₂, -C(O)NHC₁₋₆ alkyl,
 -C(O)N(C₁₋₆ alkyl)₂, -OC(O)C₁₋₆ alkyl, -NHC(O)C₁₋₆ alkyl, -S(O)_mNH₂,
 -S(O)_mNHC₁₋₆ alkyl, -S(O)_m(C₁₋₆ alkyl)₂, aryl, heteroaryl and heterocyclyl

wherein m is 0, 1, or 2,

or a pharmaceutically acceptable salt thereof, optionally in the form of a single
 stereoisomer or mixture of stereoisomers thereof.

10. The method of claim 1, where the insulin receptor-activating compound is a
 compound of Formula VI



15 Formula VI

wherein

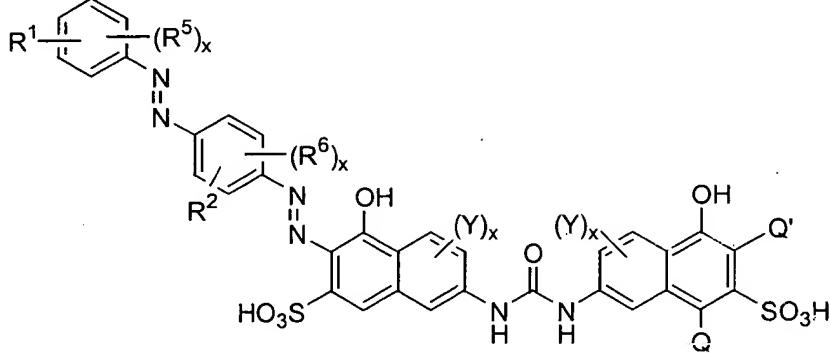
R¹ is hydrogen, or methyl

R² is -CH₂CH₃ or -CH=CH₂

R³ is -CH=CH-C(CH₃)=CH₂; CH₂-CH=C(CH₃)₂ or -CH₂-CH₂-CH=C(CH₃)₂,

20 or a pharmaceutically acceptable salt thereof, optionally in the form of a single
 stereoisomer or mixture of stereoisomers thereof

11. The method of claim 1, where the insulin receptor-activating compound is a compound of Formula VII

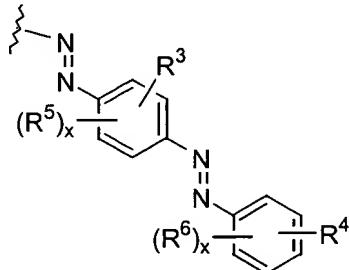


Formula VII

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wherein

Q and Q' are either hydrogen or



R¹ and R² are, independently, -SO₂NR⁷₂, -C(O)NR⁷₂, -NR⁷SO₂R⁷, -SO₂OR⁷, -C(O)OR⁷, -PO₃R⁷₂, or tetrazolyl,

10 R³ and R⁴ are, independently, -SO₂NR⁷₂, -C(O)NR⁷₂, -NR⁷C(O)R⁷, -SO₂OR⁷, -C(O)OR⁷, -PO₃R⁷₂, or tetrazolyl,

R⁵ and R⁶ are, independently, hydrogen, lower alkyl, substituted lower alkyl, cyano, halo, nitro, -SR⁸, -C(O)R⁸, -SO₂OR⁸, -OSO₂R⁸, -SO₂NR⁸₂, -NR⁸SO₂R⁸, -OC(O)R⁸, -C(O)OR⁸, -C(O)NR⁸₂, -NR⁸C(O)R⁸, -OR⁸, or -NR⁸₂,

15 each R⁷ and R⁸ is, independently, hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, aryl(lower)alkyl, substituted aryl(lower)alkyl, heteroaryl(lower)alkyl, substituted heteroaryl(lower)alkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl,

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each Y is a non-interfering substituent, and
each x is, independently, 0, 1 or 2,
or a pharmaceutically acceptable salt thereof, optionally in the form of a single
stereoisomer or mixture of stereoisomers thereof.

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12. The method of claim 1, further comprising administering a therapeutically effective amount of an additional form of treatment for insulin resistance, hyperglycemia, diabetes, ketoacidosis, lipodystrophy, or hypertriglyceridemia.

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13. The method of claim 12, wherein the therapeutically effective amount of the additional form of treatment when administered in combination with a compound of the invention is less than the amount of the additional form of treatment that would be therapeutically effective if delivered to the patient alone.

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14. The method of claim 12, wherein the additional form of treatment is insulin.

15. The method of claim 12, wherein the additional form of treatment is an insulin analog.

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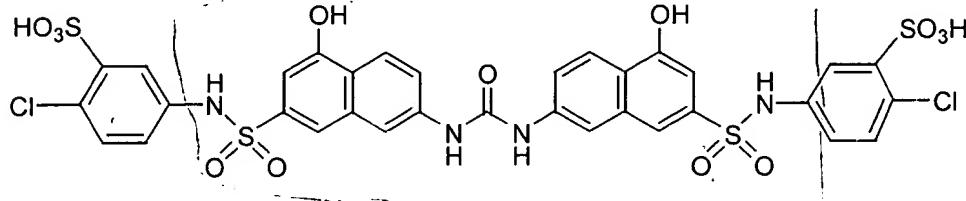
16. The method of claim 14, wherein the therapeutically effective amount of insulin or insulin analog when administered in combination with a compound of the invention is less than the amount of insulin or insulin analog which would be therapeutically effective if delivered to the patient alone.

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17. The method of claim 1, comprising administering two of the compounds of claims 3-11.

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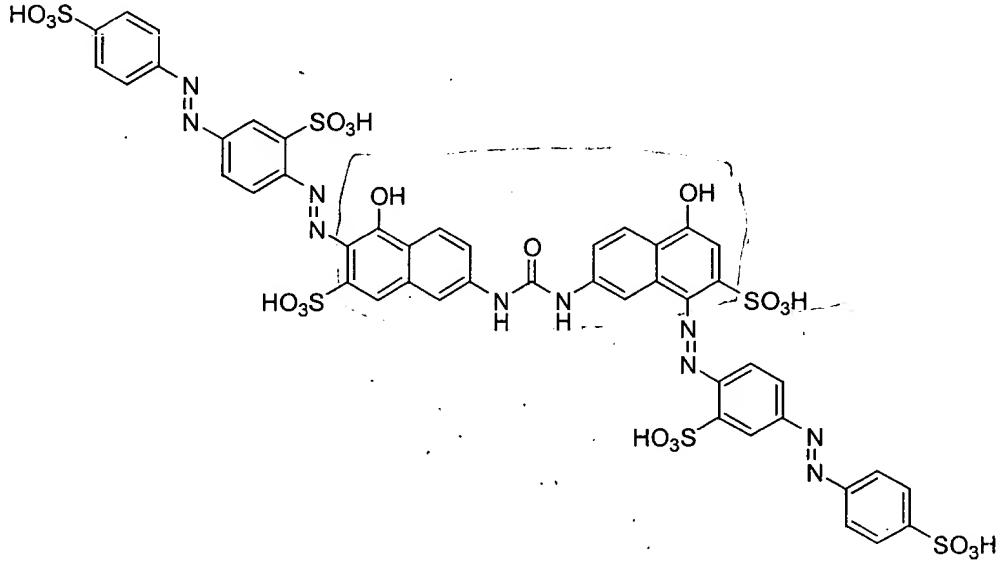
18. The method of claim 1, where the insulin receptor-activating compound is



or a pharmaceutically acceptable salt thereof.

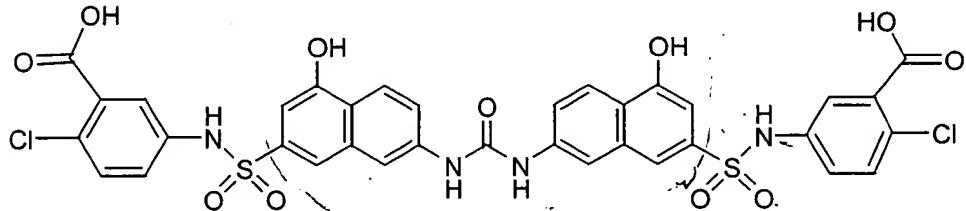
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19. The method of claim 1, where the insulin receptor-activating compound is



or a pharmaceutically acceptable salt thereof.

10 20. The method of claim 1, where the insulin receptor-activating compound is



or a pharmaceutically acceptable salt thereof.

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